REMARKS

Claims directed to model systems and methods f generating them not limited to rodents have been canceled. Applicants believe that the specification is enabling for mammalian non-human animals in general. However, to avoid any consideration that there may have been an attempt to recapture subject matter surrendered in the issued patent, these claims have been canceled. It is believed that cancellation of these claims simplifies prosecution.

Claims 1, 11, 13, 15, 20, 22, 26 and 28, all of the remaining independent claims have been amended in an identical manner to clarify that the orthotopically transplanted intact tumor must metastasize. Support for this amendment is found in the specification of the issued patent in, for instance, column 1, lines 55-67, which explain that a deficiency of prior art models is their inability to metastasize, column 7, lines 9-13, which indicate that the clinician is allowed to identify both primary *and secondary* sites of tumor growth and throughout the specification. Further, the ability of the tumors transplanted according to the method of the invention to metastasize has been repeatedly demonstrated both by the inventors and by imitators. See, for example, Furukawa, T., *et al., Cancer Res. 53* (1991) 1204-1206 and An, Z, *et al., Clin. and Exper. Metastasis* (1999) 0:1-6. The amendment to the claims thus does not constitute new matter and emphasizes the value of the present model.

Entry of the amendment is respectfully requested. Applicants understand that this entry is discretionary after final, but believe that it is helpful in placing the claims in a position for allowance.

Status of the Application

With the cancellation of claims directed to n n-rodent models or methods to prepare non-rodent models, the sole remaining issue is that of obviousness, a rejection applied to all claims

over the combination of Wang in view of McLemore, and in further view of Otto. Wang and McLemore are said to teach orthotopic transplantation of tumor cells or suspensions while Otto is said to teach transplantation of histologically intact tumors, but not orthologically. In regard to this basis for rejection, applicants wish to discuss at the interview the following considerations:

First, whether a *prima facie* case has been advanced that one of ordinary skill in the art would be motivated to combine the teachings of McLemore, Wang, and Otto.

Second, whether the very dramatic success of the model described and claimed in the application provides support for a conclusion of non-obviousness regardless of the existence of any possible *prima facie* case.

With respect to the first issue, applicants wish to draw the attention of the Office to the recently decided Federal Circuit cases on this point which make clear that there must be a teaching or motivation to combine the documents cited. It is not sufficient to assert that once combined the invention becomes obvious; there must be a motivation to make the combination in the first place and the Office must provide a rationale which supports this motivation. The only rationale that applicants see in the discussion of the rejection is that

> The skilled artisan would have been motivated to transplant human neoplastic tissue rather than human neoplastic cells in suspension in order to save the time and effort of generating and maintaining human cell lines *in vitro* that retain the characteristics of the original tumor.

Applicants respectfully dispute this framing of the motivation. There is clearly no necessity to generate and maintain human cell lines *in vitro* that maintain the characteristics of the original tumor. Instead, it would be quite possible, as described, indeed, by McLemore to propagate xenographs "derived directly from enzymatically digested, fresh human lung tumor specimens obtained at the time of diagnostic thoracotomy and representing all four major lung cancel cell

types" (see Abstract, about three-quarters of the way down). Indeed, the techniques described in the specification are actually more troublesome than those of the prior art in terms of convenience and efficiency. They are surgical techniques which require more skill than simply injecting enzymatically digested cells (or cell lines). Therefore, this asserted "convenience" cannot be the motivation to combine the documents.

Cases with respect to which applicants would request consideration include *In re Rouffet*, 47 USPQ2d 1453 (Fed. Cir. 1998) which was mentioned in the previous response as well as *In re Dembiczak*, 50 USPQ2d 1614 (Fed. Cir. 1999) and *In re Dance*, 48 USPQ2d 1635 (Fed. Cir. 1998). There are others, of course, but in each case, it is made clear as the Office, indeed, acknowledges that there must be a motivation to combine these documents absent the teachings of the invention.

Applicants have added the requirement for metastasis to the claims as the superiority of this model has repeatedly been demonstrated in terms of its ability to generate metastases. The McLemore paper cited by the Office discloses distant metastases only in 3% of the subjects used. On the other hand, as demonstrated by applicants' results in the paper by Furukawa, metastases were formed in 100% of the mice with extensive primary growth. The formation of metastases is an important part of the success of the model described and claimed.

With respect to the second matter raised - commercial success, applicants first point out that the counterpart patents to the present application in Europe and Japan have been opposed, in both cases by Takeda Chemical Co., because the model is of sufficient commercial importance that opposition has been considered useful. In both cases, the opposition has failed and claims substantially equivalent to those presented here have been upheld. In Europe, indeed, the claim

encompass model including non-human mammals in general. The details of these opp sitions can be supplied if the Office desires.

Further, it has been necessary for applicants to bring suit against infringers of the Japanese counterparts, and the use of the model, affectionately called "metamouse" has been a commercial success for the assignee. If necessary, evidence of this commercial success can be provided; however, it is believed that no *prima facie* case has actually been made out.

Applicants wish to discuss these issues at the interview.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 312762001530.

Respectfully submitted,

DRAFT

Dated: November ___, 2001 By: _____

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EXHIBIT A. - VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

1. (Twice amended) A nude mouse model for human neoplastic disease, wherein said mouse has histologically intact human neoplastic tissue of at least 1 mm^3 in size transplanted onto an organ of said mouse which corresponds to the human organ from which said tissue is originally obtained; and

has sufficient immuno-deficiency to allow said transplanted neoplastic tissue to grow and metastasize, so as to mimic the progression of the neoplastic disease in the human donor.

11. (Amended) A method of generating a nude mouse model for human neoplastic disease, said method comprising:

transplanting histologically intact human neoplastic tissue of at least 1 mm^3 in size transplanted onto an organ of a nude mouse which corresponds to the human organ from which said tissue is originally obtained; and

allowing said transplanted tissue to grow and metastasize, so as to mimic progression of the neoplastic disease in the human donor.

13. (Twice amended) A nude rodent model for human neoplastic disease, wherein said rodent has histologically intact human neoplastic tissue of at least 1 mm^3 in size transplanted onto an organ of said rodent which corresponds to the human organ from which said tissue is originally obtained; and

has sufficient immuno-deficiency to allow said transplanted neoplastic tissue to grow and metastasize, so as to mimic the progression of the neoplastic disease in the human donor.

15. (Twice amended) An immunodeficient rodent model for human neoplastic disease, wherein said rodent has histologically intact human neoplastic tissue of at least 1 mm^3 in size transplanted onto an organ of said rodent which corresponds to the human organ from which said tissue is originally obtained; and

has sufficient immuno-deficiency to allow said transplanted neoplastic tissue to grow and metastasize, so as to mimic the progression of the neoplastic disease in the human donor.

20. (Amended) A method f generating a nude rodent model for human neoplastic disease, said method comprising:

transplanting histologically intact human neoplastic tissue of at least 1 mm^3 in size onto an organ of a nude rodent which corresponds to the human organ from which said tissue is originally obtained; and

allowing said transplanted tissue to grow and metastasize, so as to mimic progression of the neoplastic disease in the human donor.

22. (Amended) A method of generating an immunodeficient rodent model for human neoplastic disease, said method comprising:

transplanting histologically intact human neoplastic tissue of at least 1 mm^3 in size onto an organ of an immunodeficient rodent which corresponds to the human organ from which said tissue is originally obtained; and

allowing said transplanted tissue to grow and metastasize, so as to mimic progression of the neoplastic disease in the human donor.

27. (Twice amended) A nude rodent model for human neoplastic disease, wherein said rodent has histologically intact human neoplastic tissue transplanted onto an organ of said rodent which corresponds to the human organ from which said tissue is originally obtained; and

has sufficient immuno-deficiency to allow said transplanted neoplastic tissue to grow and metastasize, so as to mimic the progression of the neoplastic disease in the human donor.

28. (Twice amended) An immunodeficient rodent model for human neoplastic disease, wherein said rodent has histologically intact human neoplastic tissue transplanted onto an organ of said rodent which corresponds to the human organ from which said tissue is originally obtained; and

has sufficient immuno-deficiency to allow said transplanted neoplastic tissue to grow and metastasize, so as to mimic the progression of the neoplastic disease in the human donor.